Henoch-Schönlein Purpuralı Çocuklarda Gastrointestinal Tutulumla Astım Arasındaki İlişki

Association between Henoch-Schönlein Purpura with Gastrointestinal Involvement and Asthma in Children

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ÖZ

GİRİŞ ve AMAÇ: *Henoch-Schönlein Purpurası, trombositopenik olmayan purpura, karın ağrısı, gastrointestinal kanama, artrit ve böbrek tutulumuyla giden bir küçük damar vaskülitidir. Henoch-Schönlein Purpura'lı hastalarda astım riskinde artış olduğu çalışmalarda gösterilmiş olsa da Henoch-Schönlein Purpurası'nda gastrointestinal tutulum ile astım arasındaki ilişkiyi gösteren çalışma bulunmamaktadır. Bu çalışmanın amacı, Henoch-Schönlein Purpura'lı hastalarda gastrointestinal tutulumla astım arasında ilişki olup olmadığını araştırmaktır.*

YÖNTEM ve GEREÇLER: *Çalışmaya 01.Eylül.2019 ve 01.Nisan.2020 tarihleri arasında Çocuk Nefroloji Polikliniği'ne başvuran ve Henoch-Schönlein Purpura tanısı alan 46 hasta dahil edildi. Tüm hastalar, alerjik hastalıklar açısından değerlendirilmek üzere Pediatrik Alerji Polikliniği'ne yönlendirildi. Hastalara astım tanısı Pediatrik Alerji uzmanı tarafından konuldu. Gastrointestinal tutulumu olanlarla olmayanlar astım tanısı alma açısından karşılaştırıldı.*

BULGULAR: *Çalışmaya katılan 46 Henoch-Schönlein Purpura'lı hastanın 24 (%52,2)'ünde gastrointestinal tutulum vardı. Gastrointestinal tutulumu olan 24 hastanın 14'üne (%58,3) astım tanısı konulurken, 10 (%41,7)'una astım tanısı konulmadı. Gastrointestinal tutulumu olmayan 22 hastanın 17'sinde (%77,3) astım saptanmaz iken, beşinde (%22,3) astım mevcuttu. Gastrointestinal tutulumu olan Henoch-Schönlein Purpura'lı hastalarda astım sıklığı, gastrointestinal tutulum olmayanlarla kıyaslandığında istatistiksel olarak anlamlı yüksekti (p=0,032).*

TARTIŞMA ve SONUÇ: *Bu çalışmada, Henoch-Schönlein Purpura'lı hastalarda gastrointestinal tutulumla astım tanısı arasında ilişki saptandı. Gastrointestinal tutulumu olan hastalar, astım açısından değerlendirilmek üzere Pediatrik Alerji Bölümü'ne yönlendirilmelidir.*

Anahtar Kelimeler: *astım, alerjik rinit, Henoch-Schönlein purpura, IgA vasküliti*

ABSTRACT

INTRODUCTION: *Henoch-Schönlein Purpura is a small vessel vasculitis that presents with nonthrombocytopenic purpura, abdominal pain, gastrointestinal bleeding, arthritis and renal involvement. Although an increased risk of asthma in HSP patients was demonstrated, the association between HSP with gastrointestinal involvement and asthma has yet to be reported. The present study investigates whether an association exists between gastrointestinal involvement and asthma in Henoch-Schönlein Purpura patients.*

METHODS: *The study included patients with Henoch-Schönlein Purpura who were admitted to the Pediatric Nephrology Department of the center between September 1, 2019 and April 1, 2020. All patients with Henoch-Schönlein Purpura were directed to the Department of Pediatric Allergy to be evaluated for allergic diseases. Diagnoses of asthma was made by a Pediatric Allergist. The frequency of asthma in patients with gastrointestinal involvement was compared with those with no gastrointestinal involvement.*

RESULTS: *The study included 46 patients with Henoch-Schönlein Purpura, of which 24 (52.2%) had gastrointestinal involvement. Of the 24 patients with gastrointestinal involvement, 14 (58.3%) presented with asthma, while 10 (41.7%) had no asthma. No asthma was present in 17 of the 22 patients (77.3%) with no gastrointestinal involvement, while 5 (22.7%) had asthma. A statistically significant greater frequency of asthma was noted in Henoch-Schönlein Purpura patients with gastrointestinal involvement when compared to those with no gastrointestinal involvement (p=0.032).*

DISCUSSION AND CONCLUSION: *Henoch-Schönlein Purpura with gastrointestinal involvement was found to be associated with asthma diagnosis. Patients with gastrointestinal involvement should be directed to Pediatric Allergy Departments for the evaluation of asthma.*

Keywords: *asthma, allergic rhinitis, Henoch Schönlein purpura, IgA vasculitis*

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INTRODUCTION

Henoch-Schönlein Purpura (HSP) is a small vessel vasculitis that is commonly seen in children, and is characterized by nonthrombocytopenic purpura, abdominal pain, gastrointestinal (GIS) bleeding, arthritis and renal involvement. Although HSP is usually a self-limited disease, on rare occasions, serious complications may develop, including renal impairment, intestinal perforation and central nervous system involvement (1-3).

The cause and pathogenesis of HSP has yet to be clarified. Since HSP has been reported to develop after exposure to food allergens and insect bites, it has been termed anaphylactoid purpura (4-7). Although HSP is considered to be a TH1 mediated disease, the increases in such Th2 mediated inflammatory markers as Immunoglobulin E (IgE), serum eosinophilic cationic protein and urinary leukotriene E4 levels suggest that HSP may be a Th2-mediated disease (8-11). This finding is supported by a study in which it was shown that atopic children especially with asthma are at increased risk of HSP (12).

It was demonstrated that such gastrointestinal (GI) symptoms as abdominal pain and vomiting were observed more frequently in patients with asthma (13). Association between asthma and GIS symptoms was explained by inflammation which effects both lung and GIS (14). Gastrointestinal involvement in HSP is a common finding. In the largest case series with HSP patients, reported by Esaki et al, including six patients with GI biopsies, inflammation was identified in 5/6 biopsies (15).

Henoch-Schönlein Purpura may be a Th2-mediated disease like asthma. Inflammation may play a role on GIS symptoms in both HSP and asthma patients. So, we hypothesized that HSP patients with GIS involvement would be more likely to be diagnosed with asthma.

The present study investigates allergic diseases in HSP patients, and whether an association exists between HSP with GIS involvement and asthma.

MATERIAL AND METHOD

The study included patients with HSP who were admitted to the Pediatric Nephrology Department of the center between September 1, 2019 and April 1, 2020. Approval for the study was granted by the Ethics Committee of the center (2020/331). Informed consent was obtained from the parents of the patients. Complaints at admission, GIS, renal involvement, the drugs received and hospitalization details were recorded. An HSP diagnosis was based on clinical manifestations, including nonthrombocytopenic purpura located especially in the lower extremities and buttocks, and at least one of the following: arthralgia or arthritis, abdominal pain or nephritis, based on the 1990 criteria of the American College of Rheumatology. HSP with GIS involvement was defined if the patients presented with at least one of the following: abdominal pain, vomiting, intussusception, gastrointestinal hemorrhage and presence of fecal occult blood. HSP with renal involvement was defined as having at least one of the following: Hematuria (>5 red blood cells per hpf in high power centrifuged urine) with mild (4–40 mg/m2/h) or no proteinuria, mild proteinuria, nephrotic-range proteinuria (40 mg/m2/h), elevated serum creatinine and/or hypertension. Patients with GIS and renal manifestations such as abdominal pain, intussusception, gastrointestinal hemorrhage, presence of fecal occult blood, arthritis or nephrotic-range proteinuria were hospitalized. Patients with GIS and/or renal involvement were started on steroid treatment, while those who had mild proteinuria, with or without hematuria began captopril treatment. Recurrent HSP was defined as a return of the disease three months after the first episode.

All patients with HSP were directed to the Department of Pediatric Allergy for allergy evaluations. Asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis diagnoses were made by the Pediatric Allergist, based on previous history, a physical examination and diagnostic tests, such as specific IgE of food and aeroallergens, respiratory function tests, and skin prick tests for inhalant and/or food allergens. The diagnosis of asthma was based on history of characteristic symptom patterns and evidence of variable airflow limitation, from bronchodilator reversibility testing as suggested in Global Inıtiative of Asthma (GINA) guideline 2014. Allergic rhinitis was diagnosed by history and examination, supported by specific allergy tests according to British Society of Allergy and Clinical Immunology (BSACI) guideline 2017. Allergic rhinoconjunctivitis diagnosis was based on symptoms (nasal itch/sneeze, watery discharge) on allergen exposure, often associated with rhinitis symptoms, positive skin prick test or serum-specific IgE to allergens that are relevant according to the history.16 Atopic dermatitis was diagnosed by clinical features, presence of pruritus, and chronic

or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy (17). The skin prick test for food antigens (egg white, egg yolk, cow's milk, wheat, peanut, fresh water fish, veal, walnut, chicken, cocoa) and the skin prick test for inhalant allergens (Dermatophagoides pteronyssinus, Dermatophagoides farinea, Alernaria, Clodasporium, Aspergillus, Candida albicans, tree pollens, grass pollen, weeds, cockroach) (ALK, Madrid) were performed on all patients whose parents' gave their consent. The skin prick tests were performed on the volar side of the patients' forearm according to the guidelines of the subcommittee on skin tests of the European Academy of Allergology and Clinical Immunology (EAACI). Histamine hydrochloride (1 mg/ml) and normal saline solutions were used as positive and negative controls. The skin tests were read after 15 minutes, and a wheal of at least 3 mm was accepted as a positive allergy. FX5 was defined as the serum specific IgE level of food allergens (Egg white, milk, fish, wheat, peanut, soybean). Phadiotop was defined as the serum specific IgE level of aeroallergens. FX5 and/or phadiotop positivity was defined if the result was higher than 0.35 kUA/l. Eosinophilia was defined if the eosinophil count was higher than 4% in a complete blood count. Patients with GIS and/or renal involvement were compared with controls without such conditions in terms of allergic disease.

The data analysis was conducted using SPSS 21.0 software. Descriptive statistics were presented as mean and standard deviation, and the dependency between categorical variables was tested using Pearson's Chi-square Test, Fisher Exact Chi-square Test and Continuity Correction Chi-square Test. A p value of <0.05 was considered statistically significant.

RESULTS

The study included 46 patients (25 male; 21 female) with a first diagnosis of HSP. The mean age of the patients were 8.02±3.39 (2–17). Cutaneous purpura was present in all of the patients, while other findings included arthritis/arthralgia in 24 patients (52.2%), gastrointestinal involvement in 24 patients (52.2%), renal involvement in 13 patients (28.3%), and both GIS and renal involvement in four (8.7%) patients. All of the patients with GIS involvement had abdominal pain and fecal occult blood present. No intussusceptions or massive gastrointestinal hemorrhages were observed in any of the patients. Furthermore, five patients had hematuria (10.9%), three had mild proteinuria (6.5%), and four had hematuria and mild proteinuria (8.7%). In addition, 21 patients (45.7%) were hospitalized, 22 (47.8%) patients were started on steroid treatment, and three (6.5%) were started on captopril and steroid treatment. A recurrence of HSP was observed in 13 (28.3%) patients. The findings of an allergic evaluation of the patients is presented in table 1.

Table 1. Allergic diseases and test results of the patients with HSP

Variables	**Patients (n=46)**	
	N	%
Asthma	19	41.3
Allergic rhinitis	21	45.7
Allergic conjunctivitis	6	13.0
Atopic dermatitis	2	4.3
Asthma and allergic rhinitis	10	21.7
Asthma and allergic conjunctivitis	6	13.0
Asthma and allergic rhinitis and allergic conjunctivitis	2	4.3
FX5 positivity	6	13.0
Phadiatop positivity	10	21.7
Eosinophilia	10	21.7

While 12 patients with HSP had been diagnosed with asthma before the evaluation, after the allergic examination and tests, 19 were found to have asthma (41.3%). Seven patients who were diagnosed asthma after evaluation had characteristic symptoms and reversibility was detected after bronchodilator reversibility tests. The diagnoses other than asthma such as gastroosephageal reflux, cystic fibrosis were excluded in patients with no reversibility. The median Immunoglobulin E levels of the patients were 88.5 (18–1800) U/ml. Skin prick tests for foods were positive in five of 42 patients (11.9%), of whom two had cow's milk, two had whole egg and one had multiple food allergies. The skin prick tests for inhalant allergens were positive in 10 of the 37 patients (27.0%) of whom

three had mites, six had multiple aeroallergens and one had pollen allergies. The associations between patients diagnosed with GIS involvement, renal involvement, recurrent HSP and asthma are presented in table 2.

Table 2. The association between GIS, renal involvement, recurrent HSP and asthma diagnosis in HSP patients

Variables	Asthma (n=19)				p
	No	%	Yes	%	
GIS Involvement (n=24)	10	41.7	14	58.3	**0.032**
Renal Involvement (n=13)	9	69.2	4	30.8	0.563
GIS and Renal Involvement (n=4)	2	50	2	50	1.000
HSP Recurrence (n=13)	9	69.2	4	30.8	0.582

Of the 24 patients with GIS involvement, 14 (58.3%) presented with asthma, while 10 (41.7%) had no asthma. No asthma was present in 17 of the 22 patients (77.3%) with no GIS involvement, while 5 (22.7%) had asthma. The number of patients with asthma was statistically significantly greater in the HSP patients with GIS involvement than in those with no GIS involvement (p=0.032). The difference in the frequency of asthma in patients with renal involvement and with recurrent HSP, and in those without these conditions, was not statistically significant (p=0.563, 0.582 respectively). No statistically significant difference was observed between the patients with GIS involvement, renal involvement or recurrent HSP in terms of allergic rhinitis diagnosis when compared those without such conditions (Table 3) (p=0.747, 0.710, 1.000 respectively).

Table 3. The association between GIS, renal involvement, recurrent HSP and allergic rhinitis diagnosis in HSP patients

Variables	Allergic Rhinitis (n=21)				p
	No	%	Yes	%	
GIS Involvement (n=24)	12	50.0	12	50.0	0.747
Renal Involvement (n=13)	6	46.2	7	53.8	0.710
GIS and Renal Involvement (n=4)	1	25.0	3	75.0	0.318
HSP Recurrence (n=13)	7	53.8	6	46.2	1.000

No association was identified between GIS, renal involvement, HSP recurrence and atopic dermatitis diagnosis (p=0.223, 1.000, 1.000 respectively). All of the patients diagnosed with allergic conjunctivitis had GIS involvement (n=6) (Table 4).

Table 4. The association between GIS, renal involvement, recurrent HSP and allergic conjunctivitis diagnosis in HSP patients

Variables	Allergic Conjunctivitis (n=6)				p
	No	%	Yes	%	
GIS Involvement (n=24)	18	75.0	6	25.0	0.110
Renal Involvement (n=13)	8	61.5	5	38.5	0.565
GIS and Renal Involvement (n=4)	2	50.0	2	50.0	1.000
HSP Recurrence (n=13)	11	84.6	2	15.4	0.571

No statistically significant difference was noted between those with renal involvement or recurrent HSP in terms of allergic conjunctivitis when compared to those without such conditions (p=0.065, 1.000 respectively). There was no association between skin prick test positivity for foods and GIS involvement in HSP patients (P=1.000). No association was found between HSP with GIS involvement and FX5 positivity (p=0.664), phadiatop positivity (p= 0.281) or eosinophilia (p=1.000). There was no association identified between HSP recurrence and asthma, allergic rhinitis, GIS or kidney involvement (p=0.376, 0.892, 0.426, 0.155 respectively).

DISCUSSION

This is the first study to investigate the association between GIS involvement and allergic diseases in patients with HSP. The findings reveal that HSP children with GIS involvement were more commonly diagnosed with asthma than those without such conditions. This finding indicates the importance of evaluating patients with GIS involvement for asthma.

National studies have shown the prevalence of asthma in Turkish children to be 2–16%.(18-21) In different national studies, the prevalence of allergic rhinitis has been reported to be 8.1—to 23.5%.(21-25) In the present study asthma and allergic rhinitis frequency was found to be high (41.3%, 45.7% respectively) in HSP patients when compared to the normal population. In a population-based study, it

was demonstrated that children with allergic diseases, including allergic rhinitis, asthma and atopic dermatitis, were at increased risk of developing HSP.26 Furthermore patients with atopic dermatitis were shown to be at an increased risk of developing HSP and HSP with renal involvement (12). Furthermore, increase in Th2-mediated markers, such as elevated serum IgE, serum ECP and urinary leukotriene E4 levels, support the suggestion that HSP could be a Th2-mediated disease (8-11). As Th2-mediated immune mechanisms are responsible for both allergic diseases and HSP, allergic diseases may be more common in patients with HSP.

It was found that patients with asthma more often developed gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain than the heathy controls. Furthermore, gastrointestinal symptoms were more common in atopic symptoms other than asthma, or with positive skin prick tests for foods.13 A systematic review and meta-analysis found that patients with asthma were more likely to have concurrent gastrointestinal conditions, although the association between two has yet to be identified (27). The effects of food allergies on patients with asthma and irritable bowel syndrome (IBS) are controversial. While some studies have identified no correlation between skin prick tests for foods and irritable bowel syndrome (28-29), in another study, positive skin test results for foods were significantly more common in IBS patients than in controls (30). The association between asthma and GIS symptoms has been explained by the inflammatory etiology that affects both the lungs and GIS(14) due to the activated lymphocyte migration from bronchial mucosa lymphoid tissue to the intestinal mucosa (13). In the present study, those with HSP with GIS involvement were more often diagnosed with asthma. This may be related to the inflammation that affects the vessels, lungs and intestinal mucosa. Positive skin tests for foods were not more common in patients with GIS involvement than in those without GIS involvement in the present study.

The risk factors for the recurrence of HSP have been investigated in many studies. In a study of allergic rhinitis with renal involvement, patients who received steroid treatment for >10 days were identified as at greater risk of HSP recurrence (31). Joint and GIS involvement were shown to be predictive of an HSP relapse in another study (32). Persistent rash over a period of 1 month was found to be a predictor of disease relapse (33). No association was found between HSP relapse and GIS, renal involvement or allergic disease in the present study.

The limitations of the study include the low number of patients and its single center design. Multicenter studies may provide more detailed information about the association between GIS involvement and allergic diseases in patients with HSP.

Conclusions

In conclusion, HSP with GIS involvement was found to be associated with an asthma diagnosis. Patients with GIS involvement should be directed to the Pediatric Allergy Department for evaluation of asthma.

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